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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 29

Serial Number: 08/444,934
Filing Date: May 22, 1995
Appellant(s): Richard M. Lawn, Gordon A. Vehar, and Karen L. Wion

Patrea L. Pabst, Reg. No. 31, 284

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed October 14, 1999.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of claims.*

The statement of the status of claims contained in the brief is correct.

Upon reconsideration, the Examiner notes that Claims 5, 29, 32, 33, and 37 are drawn to full-length tissue factor proteins and tissue factor proteins lacking the transmembrane domain which are fully described in the specification. These Claims are presently dependent from rejected claims, however, they would be allowable if rewritten in independent form.

Therefore, the correct statement of the status of the claims is as follows:

This appeal involves Claims 4, 6, 8, 20, 21, 23, 27, 28, 31, 34-36, and 38-41.

Claims 24 and 25 are allowed.

Claims 5, 29, 32, 33, and 37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Claims 1-3, 7, 9-19, 22, 26, and 30 have been canceled.

(4) *Status of Amendments After Final.*

No amendment after final has been filed.

(5) *Summary of invention.*

The summary of invention contained in the brief is correct.

(6) ***Issues.***

The appellant's statement of the issues in the brief is correct. However, as indicated in Section 3 of this Examiner's Answer, Claims 5, 29, 32, 33, and 37 are drawn to allowable subject matter.

(7) ***Grouping of claims.***

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because all claims on appeal (Claims 4, 6, 8, 20, 21, 23, 27, 28, 31, 34-36, and 38-41)are directed to tissue factor variants having amino acids 1-219 or having amino acid residues 1 to between 219 and 263. The issue in the appeal is whether the specification as originally filed describes this specific tissue factor variant. Thus, all of the claims on appeal would stand or fall together.

(8) ***Claims appealed.***

The copy of the appealed Claims contained in the Appendix to the brief is correct.

(9) ***Prior Art of record.***

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal:

1. Spicer et al. PNAS 84: 5148-5152.

2. Scarpati et al. Biochemistry 26: 5234-5238).

3 Fisher et al. Thrombosis Research 48: 89-99.

(10) *New prior art.*

No new prior art has been applied in this examiner's answer.

(11) *Grounds of rejection.*

The following ground of rejection is applicable to the appealed claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 4-6, 8, 20-21, 23, 27-29, 31-36, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses the complete amino acid and cDNA sequence of human tissue factor protein. In addition, the

specification and the original claims describe in clear and specific detail a variant of the tissue factor protein wherein amino acids 220-242, which define the transmembrane domain, are deleted. However, the specification does not describe or even suggest making a variant of tissue factor consisting of a tissue factor having from at least amino acid 1 to at least amino acid 219 or a tissue factor having an amino acid sequence from between amino acid 1 to between residues 220-263.

The tissue factor protein consists of 263 amino acids. The extracellular domain (denoted ECD in figure below) is located at the amino terminus and is made up of residues 1-219; the transmembrane domain (denoted TMD in figure below) comprises amino acid residues 220-242; and the intracellular domain (denoted ICD in figure below) comprises amino acid residues 242-263 at the carboxy terminus. Diagrammatically, then, the tissue factor protein can be depicted as follows:

NH_2-[----------ECD----------|--TMD--|--ICD--]-COOH

It is the Examiner's position that the specification does not teach that the extracellular domain (amino acid residues 1-219) of tissue factor protein should be made or used by itself. Rather, the specification teaches to <u>delete</u> the transmembrane domain or hydrophobic portion of the tissue factor protein. The

soluble tissue factor protein structure described in the specification is depicted as follows:

|--------------------ECD--------------------|--ICD--|

Basis for the soluble protein structure as depicted above is found in the specification. All remarks in the specification regarding deletional variants of tissue factor protein are listed below, emphasis being used to highlight precise statements.

At page 1, line 30, the specification states that:

> This invention is also directed to tissue factor protein derivatives, particularly derivatives **lacking the near C-terminal hydrophobic portion of the protein**, and their production by recombinant DNA techniques.

At page 7, line 10, the specification states that:

> This invention is further directed to novel tissue factor protein derivatives, in particular derivatives **lacking** the signal sequence and **the hydrophobic portion of the protein near the C-terminal end of the protein comprising the amino acid sequence which constitutes the tissue factor protein transmembrane or membrane binding domain.**

At page 9, in the legend for Fig. 5, the specification states that:

> The predicted **hydrophobic membrane spanning domain encompasses residues 220-243** and is indicated by the filled bar.

At the paragraph bridging pages 12-13, the specification states:

> Deletions are characterized by the removal of one or more amino acid residues from the tissue factor protein sequence. Typically, **no more than about from 2 to 6 residues are deleted at any one site** within the tissue factor protein molecule, although deletion of residues -31 to -1 inclusive will be undertaken to obtain met-tissue factor protein, a variant adapted for intracellular direct expression of met-tissue factor protein. **Another deletion is of the transmembrane domain located at about residues 220 to 242 of the tissue factor protein molecule.**

At page 14, paragraphs 1 and 2, the specification states:

> A major class of substitutional or **deletional variants are those involving the transmembrane, i.e. hydrophobic or lipophilic region of the tissue factor protein.** The **transmembrane region of the tissue factor protein is located at about residues 220 to 242** of the protein encoded by the DNA from human adipose tissues. This region is a **highly hydrophobic or lipophilic domain that is the proper size to span the lipid bilayer of the cellular membrane.** It is believed to anchor tissue factor protein in the cell membrane.
>
> **Deletion or substitution of the transmembrane domains will facilitate recovery and provide a soluble form of recombinant tissue factor protein** by reducing its cellular or membrane lipid affinity and improving its water solubility so that detergents will not be required to maintain tissue factor protein in aqueous solution. **Preferably, the transmembrane domain is deleted**, rather than substituted in order to avoid the introduction of potentially immunogenic epitopes. **One advantage of the transmembrane deleted tissue factor protein** is that it is more easily secreted into the culture medium. This variant is water soluble and does not have an appreciable affinity for cell membrane lipids, thus considerably simplifying its recovery from recombinant cell culture.

These five passages omit reference to truncating the tissue factor protein at the hydrophobic portion and, without inclusion of any statement regarding the deletion of the hydrophilic intracellular domain, these passages specify that only the hydrophobic portion (residues 220-243) should be removed from the tissue factor protein. Also, while one skilled in the art would generally understand that a soluble portion of a membrane-bound protein is its extracellular domain, it should be noted that the extracellular domain and the intracellular domain are hydrophilic and therefore deletion of the transmembrane domain alone will result in a soluble protein. The specification is clear that the transmembrane domain is to be deleted from the tissue factor protein. The specification does not indicate that the tissue factor protein should be truncated at the transmembrane domain or that both the transmembrane domain and the intracellular domain should be deleted, resulting in the extracellular domain being by itself.

Further, the specification does not provide for any tissue factor protein fragment of 219 amino acids which may provide basis for the extracellular domain being by itself.

At page 13, line 10, the specification states:

> However, variant tissue factor protein **fragments having up to about 100-150 residues** may be conveniently prepared by *in vitro* synthesis.

Additionally, the removal of both the transmembrane domain and the intracellular domain together (44 amino acid residues in length) from the tissue factor protein is not supported by the specification because deletions are limited to about 1-30 residues and not 44 residues.

At page 13, line 30, the specification states:

...and **deletions will range about from 1 to 30 residues**....

Therefore, the specification teaches to delete the transmembrane domain of the tissue factor protein and there is no basis in the specification for making the extracellular domain of the tissue factor protein alone.

(12) New Ground of rejection

This Examiner's Answer does not contain any new ground of rejection.

(13) *Response to argument.*

Invention must be clearly conveyed to those skilled in the art

On page 10 of the Appeal Brief, Appellants cite case law and a passage from MPEP 2163.02 to support their argument that the subject matter of a claim need not be described literally but merely needs to have been conveyed to those skilled in the art. The Examiner agrees that the subject matter does not "need to be

described literally" however the invention must be "*clearly conveyed to those skilled in the art at the time the application was filed*". The word "convey" means "to make known, to communicate" and in the present case the application simply has failed to clearly make known that the invention included a tissue factor variant having the extracellular domain alone. As illustrated in Section 11 (pages 6-8) of this examiners answer, the specification, time and again, specifically describes a variant wherein only the hydrophobic transmembrane domain is deleted. Moreover, original claims 5 and 8 provide additional evidence that a tissue factor variant wherein the transmembrane domain is deleted (original claim 5) or wherein "the amino acid residues about 221 to 241 are deleted" (original Claim 8). The specification does not discuss and the original claims lack a tissue factor variant truncated at amino acid 219, or a tissue factor variant comprising the extracellular domain, or a tissue factor having an amino acid sequence from amino acid residue 1 to amino acid residue 219. A tissue factor variant having only an extracellular domain was not clearly conveyed in the application as originally filed.

Ralston Purina Co. v. Far-Mar-Co.

On page 11 of the Appeal Brief, Appellants cite Ralston Purina Co. v. Far-Mar-Co. (277 U.S.P.Q. 177 (Fed. Cir. 1985)) to

assert that as long as one of ordinary skill in the art would recognize lower boundaries of some defined range as describing a lower limit, an open ended claim is sufficiently described if a naturally occurring upper boundary would be understood by the ordinary skilled person.

The Ralston Purina Co. v. Far-Mar-Co. is distinct from the present situation because the claim limitations were directed to a step in a process wherein as long as the critical lower temperature boundary was disclosed, the range of upper boundary did not change the process. In the present case, the issue is whether or not a specific variant is disclosed. Appellants go to great detail in the specification and original claims to describe non-glycosylated variants, variants containing deletions of cysteines, deletions of protease cleavage sites, and deletion of the transmembrane domain but never mention the distinct variant truncated at the transmembrane domain. The tissue factor variant lacking the transmembrane domain and cytoplasmic domain is a different product than the variant only lacking the transmembrane domain and the former of the two variants was never described in the specification.

In re Winkhaus applies to the present case

On page 12 of the Appeal Brief, Appellants argue that In re Winkhaus, 188 U.S.P.Q 129 (CCPA 1975)does not apply to the present situation because the issue in In re Winkhaus is whether

or not the claimed subject matter would have been obvious from reading the specification whereas the issue in the present case is what the description means to one of skill in the art.

It is the Examiners position that In re Winkhaus applies to the present situation. In both In re Winkhaus **and** the present case, the specification as filed does not explicitly disclose the claimed subject matter but in both cases it is argued that the claimed subject matter is apparent in the specification.

It is clear that in the present case, the specification as originally filed fails to specifically state that a tissue factor variant having amino acids 1-219 or having amino acids 1 to between 219 and 263 was part of the invention at the time the application was filed. However, Appellants argue the Konigsberg Declaration indicates that such a variant is apparent from the description of a variant lacking the transmembrane domain. The following passages from the Konigsberg Declaration (emphasis added) illustrate that the claimed variant is not explicitly described in the specification but only is apparent from a description of a deletion of the transmembrane domain (amino acids 219-242):

Konigsberg states at page 3, line 4:

> I believe that those of skill in the arts of proteins, cloning and expression, and tissue factor at that time **would have understood the description** of deletion of the transmembrane region to tissue factor to include tissue factor protein from which the entire C-terminal

> region, including the transmembrane and cytoplasmic regions, had been deleted. This is so because the deletion of the transmembrane region as described in the specification would have been viewed and understood as an ***indication*** that the extracellular domain could be used separately from the transmembrane region and the cytoplasmic region.

> At the top of page 4, Konigsberg states that:

> ...it is clear, and those of skill in the art at the time **would have understood**, that deletion of the transmembrane region **is equivalent to** deletion of both the transmembrane region and the cytoplasmic region, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain. For these reasons, it is my opinion that those of skill in the art at the time the application was filed **would have considered** the reference to deletion of the transmembrane region **to indicate** that the inventors contemplated deletion of the C-terminal portion of the tissue factor, including the cytoplasmic domain.

Clearly, the Konigsberg Declaration does not state that the specification in the present case explicitly describes a tissue factor variant having amino acids 1-219 or amino acids 1 to between 219 and 263. The Konigsberg declaration only indicates that such a variant **would have been considered** from the description of deletion of amino acids 219-242 which make up the transmembrane domain.

> As stated in the courts:

> Although it may be *apparent*, as appellants argue, that the vapors...could be utilized for heating the mixture..., that does not mean that such a step is *described* as part of their invention. (In re Winkhaus 188 U.S.P.Q. 129 at 131 (CCPA 1975)).

Thus, In re Winkhaus, applies in the present situation because like the case of In re Winkhaus, the present application simply does not describe a tissue factor variant having the extracellular domain by itself as part of the invention and Appellants have only argued that such a variant would **have been considered**.

The Specification does not support a tissue factor variant lacking both the transmembrane domain and the intracellular domain.

Tissue factor variants

On Pages 13 and 14 of the Appeal Brief, Appellants point to specific pages in the specification which they believe to provide support for the claimed tissue factor variants. A summary of the cited passages appears below:

1) page 6, lines 10-13: discuss that the invention makes it possible to produce tissue factor derivatives but this passage does not describe any specific variants.

2) page 6, lines 18-27: states that the invention is directed to compositions and methods of producing tissue factor via recombinant DNA technology but does not describe any specific tissue factor variants.

3) page 9, lines 12-25: describes figure 5 which is a hydropathy profile and predicts that the hydrophobic membrane spanning

domain encompasses residues 220-243 but does not describe tissue factor variants.

4) page 13, lines 4-5: "another deletion is of the transmembrane domain located at about residues 220-242 of the tissue factor protein molecule". This passage only supports the tissue factor variant containing a deletion of the transmembrane domain not both the transmembrane domain and the intracellular domain.

5).

Figure 5

Appellants argue that specific support for the recited amino acid sequence (from amino acid 1 to amino acid 219) is provided by Figure 5. Figure 5 shows a hydropathy profile and a bar illustrating the boundaries of the individual domains of the tissue factor protein. While the examiner agrees that one of skill in the art would understand what those boundaries mean and that such a diagram would make it obvious to make a tissue factor variant containing only the extracellular domain, the specification does not convey that such a variant was part of the invention. The figure shows the entire tissue factor protein with regions that are hydrophilic and hydrophobic and defines the amino acids that are predicted to define a hydrophilic extracellular domain, a hydrophobic transmembrane domain, and a hydrophilic intracellular domain. The figure does not show variants of the tissue factor protein and thus does not convey to

one of skill in the art that the inventors had possession of a tissue factor protein variant lacking the transmembrane domain and the intracellular domain at the time the application was filed.

Modification of variant having extracellular domain

With respect to Appellants arguments citing support for claims 34-40 (page 14, second paragraph of Appeal Brief), the Examiner agrees that the specification supports a recombinant human tissue factor which is not glycosylated, which is expressed in non-human cells, which includes a carboxy terminal fusion, wherein the cysteine residues are substituted, wherein the proteolysis sites are deleted or substituted, and wherein an N-or O-glycosylation site is substituted or deleted. All of these modifications were specifically addressed in the specification. However, claims 34-40 depend from Claim 31 which is drawn to a tissue factor variant expressed from a nucleotide sequence encoding an amino acid sequence comprising from amino acid residue one to amino acid residue 219 as provided in Figure 2 and the specification does not convey that the invention includes such a variant. Therefore, the specification does not convey that the invention includes such a variant with the claimed modifications.

Common Sense

Appellants argue that the preferred way to delete the transmembrane domain was to make a DNA construct that simply

stopped at amino acid 219 (last paragraph of page 14 of the Appeal Brief), thereby deleting both the transmembrane domain and the cytoplasmic domain.

Once again, "this preferred way" is not disclosed in the specification.

In response to the argument that it "makes no sense" to make a tissue factor variant lacking the transmembrane domain alone, the Examiner notes that Appellants originally claimed (original Claims 5 and 8) and continue to claim (Pending Claims 32 and 33) such tissue factor variants specifically lacking residues 220-242 (the transmembrane domain alone).

Specification only describes variants lacking the **hydrophobic** region of the tissue factor protein

On page 15-16 of the Appeal Brief, Appellants cite page 14 of the specification to urge that deletions "involving" the transmembrane domain include deletion of other amino acid residues. The cited statement and surrounding passage is cited above and again here below with emphasis:

> A major class of substitutional or **deletional variants are those involving the transmembrane, i.e. hydrophobic or lipophilic region of the tissue factor protein.** The **transmembrane region of the tissue factor protein is located at about residues 220 to 242** of the protein encoded by the DNA from human adipose tissues. This region is a **highly hydrophobic or lipophilic domain that is the proper size to span the lipid bilayer of the**

> **cellular membrane**. It is believed to anchor tissue factor protein in the cell membrane.

In no place does the specification teach to delete the intracellular domain. Indeed, this passage is directed solely to the deletion of the transmembrane domain.

Application defines domains but does not convey that the invention includes a variant having amino acids 1-219.

On page 16 of the Appeal Brief, Appellants argue that Figure 5 provides a hydropathy profile of the full length tissue factor protein and the filled bar indicates the predicted amino acid residues which make up the transmembrane domain. While the boundaries of the individual domains of the protein are predicted in the figure, the figure does not convey that the invention includes a tissue factor variant having only amino acids 1-219.

Konigsberg Declaration

The Examiner agrees that the statements in the Konigsberg Declaration regarding the function of the individual domains of a transmembrane domain protein are factual statements based on the knowledge of one of skill in the art. However, as explained above, Dr. Konigsberg only concludes from this:

> "...it is clear, and those of skill in the art at the time **would have understood**, that deletion of the transmembrane region **is equivalent** to deletion of both the transmembrane region and the cytoplasmic region, since the cytoplasmic region serves no purpose in the absence of the transmembrane domain" (Konigsberg Declaration, page 5, emphasis added).

The Examiner has not dismissed factual statements of the declaration. On the contrary, the Examiner has considered and agrees with Dr. Konigsberg's statement of the function of transmembrane domains. However, the Konigsberg Declaration does not state that the specification in the present case describes a tissue factor variant having amino acids 1-219 or amino acids 1 to between 219 and 263. The Konigsberg declaration only indicates that such a variant **would have been considered** from the description of deletion of amino acids 219-242 which make up the transmembrane domain. This does not demonstrate that this variant is inextricably disclosed.

Appellants argue that "in a case such as this where the issue is not whether the subject matter is discussed at all, but rather is whether the subject matter is discussed specifically, must provide reasons why the claimed subject matter would not be understood by one of ordinary skill in the art as being described" (page 20 of the Appeal Brief).

As indicated in the Office Action mailed 7/26/98 (Paper No. 30) and cited below:

> The Declaration asserts that one of skill in the art would understand that the transmembrane domain would include residues from the C-terminal region. This argument actually confuses the issue. At the time the invention was made one of skill in the art would have assumed a transmembrane domain to be a hydrophobic region, usually situated between an extracellular and a cytoplasmic domain.
>
> Spicer et al. (PNAS 84: 5148-5152) describe the primary structure of human tissue factor. Spicer et al. teach that the protein sequence consists of three distinct domains: the extracellular (residues 1-219), the hydrophobic (residues

220-242), and the cytoplasmic (residues 243-263). See abstract. There is nothing to suggest that the hydrophobic or transmembrane domain includes residues from the C-terminal cytoplasmic domain.

Scarpati et al. (Biochemistry 26: 5234-5238) describe the cDNA sequence encoding human tissue factor. Scarpati et al. also describe the primary sequence and structure of the protein. The predicted sequence consists of a signal peptide of 32 or 34 amino acids, a probable extracellular domain of 217 or 219 amino acids, a transmembrane domain of 23 amino acids, and a cytoplasmic domain of tail of 21 amino acids. See abstract, page 5236. The reference provides no suggestion that the transmembrane domain includes residues from the C-terminal cytoplasmic domain.

Fisher et al. (Thrombosis Research 48: 89-99)also describe the cloning and expression of human tissue factor cDNA. The reference teaches that the protein contains a hydrophobic membrane spanning domain consisting of residues 220-243. The reference states, "We propose that this region, encompassing amino acids 220-243, comprises the membrane anchoring domain of tissue factor." See paragraph bridging pages 94-95. Fisher et al. do not suggest in any way that the membrane spanning domain includes residues from the C-terminal region.

Therefore, based on the teachings of Spicer et al. Scarpati et al., and Fisher et al., there is no reason, based on the state of the art at the time the invention was made, to conclude that the "transmembrane domain" included anything other than residues 220-243" (paragraphs bridging pages 5-6, Office Action mailed 7/24/98).

Based on the state of the art and the publications at the time the invention was filed, it is concluded that the transmembrane domain consists of residues 220-243 and thus reference to "deletion of the transmembrane domain" would have been understood to mean residues 220-243 and no others.

The Diagnostics Stago Opposition

As indicated in the Advisory action, Appellants present arguments found convincing in the corresponding European patent application, Opposition by Diagnostica Stago. The Examiner has read this Opposition. The discussion is too limited for the Examiner to determine why the European examiner accepted the deletion of the transmembrane domain in tissue factor protein to include the intracellular domain.

(14) *Period of response to new ground of rejection.*

In view of the absence of any new ground of rejection, prosecution remains closed.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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